(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 1 734 039 A1

(12) EUROPEAN PATENT APPLICATION

(43) Date of publication:
20.12.2006 Bulletin 2006/51

(21) Application number: **05012616.8**

(22) Date of filing: **13.06.2005**

(51) Int Cl.:
C07D 295/12 (2006.01) *C07C 275/40* (2006.01)
C07D 249/12 (2006.01) *C07D 285/08* (2006.01)
C07D 295/22 (2006.01) *C07D 251/52* (2006.01)
C07D 495/04 (2006.01) *C07D 471/08* (2006.01)
A61K 31/17 (2006.01) *A61K 31/53* (2006.01)
A61P 25/28 (2006.01)

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU MC NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR LV MK YU

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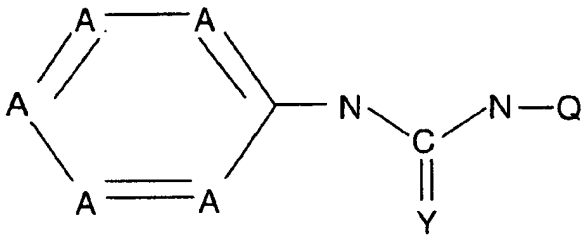
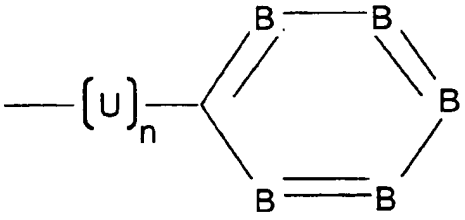
(54) Aryl urea compounds as BETA-secretase inhibitors

(57) It has been found that compounds of formula I



(I)

wherein
A is N or CR,Y is O or S and
Q is an aromatic group or an araliphatic group having the following formula



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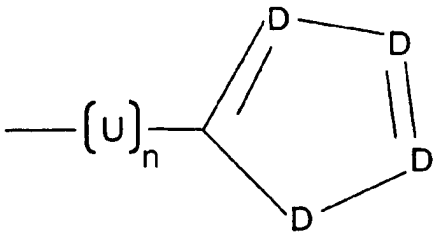
wherein
B = N or CR',
or Q has the following formula



wherein
D = O or S or N or NR_4 or CR_5
are good β-secretase inhibitors for the treatment of Alzheimer's disease.

Description

Field of the Invention

[0001] This invention relates to aryl urea and aryl thiourea compounds, in particular to such compounds acting as beta-secretase inhibitors.

Background Art

[0002] Alzheimer's disease (AD) is the most common form of dementia among older people, and affects parts of the brain that control thought, memory and language. Susceptibility to Alzheimer's disease increases with age, but Alzheimer's disease is not a normal part of the ageing process.

[0003] A characteristic of this disease is the presence of extracellular senile plaque, the major component of which is the β-amyloid peptide (Aβ). The hydrophobic, 39-43-amino-acid-long Aβ peptide is excised from the amyloid precursor protein (APP) by sequential cleavage by the so-called β- and γ-secretases.

[0004] Known genetic predispositions for AD mostly affect genes involved in Aβ generation or Aβ deposition. Since the Aβ peptide seems to play an important role in the pathogenesis of AD, current therapeutic strategies often focus on inhibition of Aβ deposition and generation. Inhibition of β-secretase activity represents an attractive option to achieve this goal.

[0005] Despite major efforts to identify novel β-secretase inhibitors by applying in vitro high-throughput screening (HTS) assays with purified soluble BACE-1 fragments and fluorogenic peptide substrates, the best progress towards efficient BACE-1 inhibition has been achieved so far by the use of peptidic transition-state mimetic compounds. However, for efficient inhibition of β-secretase in cells, their molecular weight must be reduced and their structure modified so as to allow for permeation of cellular membranes, the blood-brain barrier and for activity in the natural cellular environment.

[0006] There also exist some assays for identifying low molecular weight inhibitors of secretases that can block these membrane-bound enzymes at the natural location within intracellular compartments. Cell-based HTS assays, however, are generally faced with the problem that selection signals are often caused by compounds that interfere with cellular processes or pathways that are redundant with that of the target. For example, some compounds found by mammalian cell based assays impair the production of Aβ through the increase of the pH in intracellular compartments, or they function through protein phosphorylation, or they simply catalyze polymerization of Aβ, thus reducing the percentage of soluble peptide.

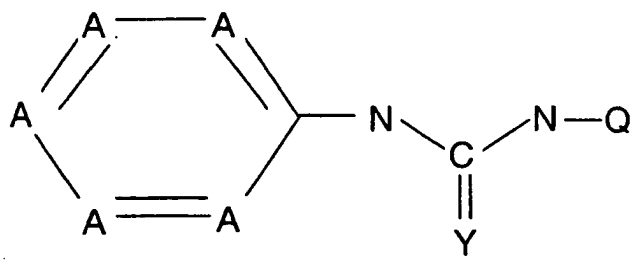
[0007] Some candidate compounds for inhibiting the production of Aβ peptide in a biological system have been proposed in US 5,814,646 and US 5,624,937.

[0008] Nevertheless, there is still a need for potent β-secretase inhibitors that directly inhibit β-secretase.

Disclosure of the Invention

[0009] Hence, it is a general object of the invention to provide compounds that directly act as β-secretase inhibitors.

[0010] Now, in order to implement these and still further objects of the invention, which will become more readily apparent as the description proceeds, the β-secretase inhibitors of the present invention are manifested by the following formula I

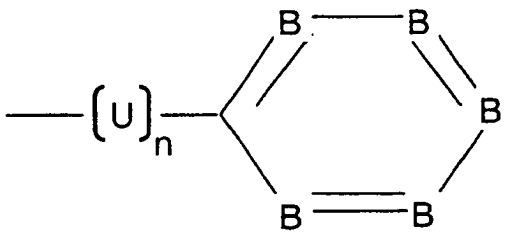


(I)

wherein

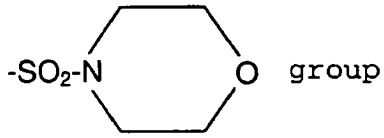
wherein

A = N or CR wherein
R is independently from each other selected from H, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, e.g. CF_3, C_1-C_6-alkyl-carbonyl, halogen, an -NR_2R_3 group
wherein R2 and R3 are independently from each other H, linear or branched C1-C6-alkyl, in particular linear or branched C1-C4-alkyl, or R2 and R3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, e.g. a piperidino, a piperazino or a morpholino group, and wherein
Y = O or S,
Q = an aromatic group or an araliphatic group having the following formula

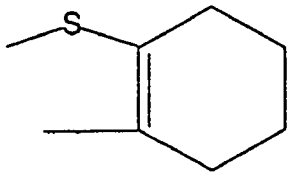


wherein

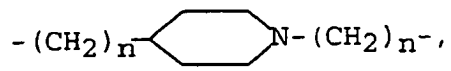
B = N or CR', wherein
R' is independently from each other selected from the group comprising hydrogen, halogen, in particular F, a C_1-C_6-alkyl group, in particular a C_1-C_4-alkyl group, an -NR_2R_3 group wherein R2 and R3 are independently from each other H, linear or branched Cl-C6-alkyl, in particular linear or branched C1-C4-alkyl, or R2 and R3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, e.g. a piperidino, a piperazino or a morpholino group, an amido group, an ester group, a



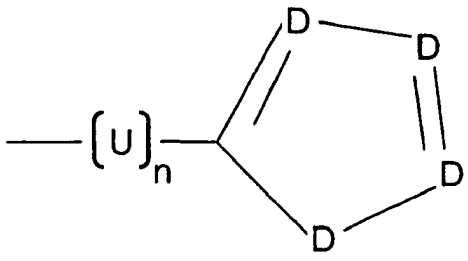
or two adjacent R' form a group



U = -CH_2-, C=O, -$(CH_2)_n$S-, -$(CH_2)_n$O-, -$(CH_2)_n$NH-, or



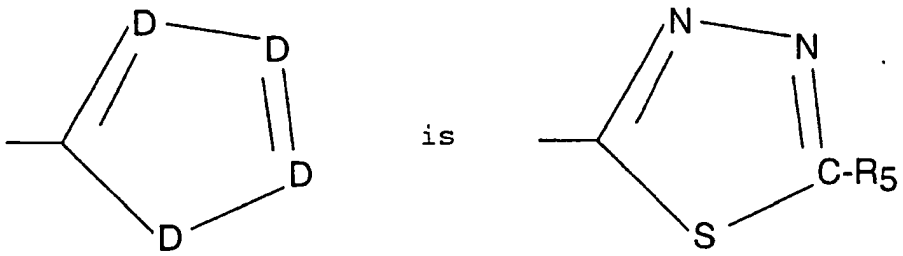
wherein the heterocycle is optionally substituted, in particular by one or two C_1-C_4-alkyl groups or such that a bicycle is formed, and
n independently from each other is 0, 1 or 2,
or Q has the following formula



wherein

D = O or S or N or NR_4 or CR_5, wherein
R_4 is linear or branched C_1-C_6-alkyl, in particular C_1-C_4-alkyl
R_5 is independently from each other selected from C_1-C_6-alkylthio, aryl-C_1-C_6-alkylthio, aryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, alkyloxy-C_1-C_6-alkyl, alkylthio-C_1-C_6-alkyl, C_1-C_6-alkyloxy, aryl-C_1-C_6-alkyloxy and optionally substituted linear or branched C_1-C_6-alkyl,
U and n are as defined above,

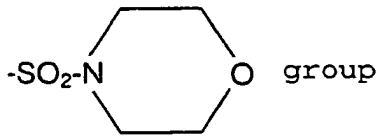
or pharmaceutically acceptable salts thereof,
with the proviso that in the case that n is 0 and



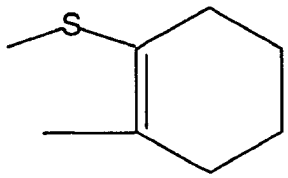
[0011] R_5 is substituted linear or branched C_1-C_6-alkyl, preferably linear or branched C_1-C_4-alkyl, with the substituent being selected from O-R_{13} or S-R_{13} or N-$R_{13}R_{13}$'with R_{13} and R_{13}' being independently selected from the group consisting of unsubstituted or substituted 5- or 6-membered aryl, unsubstituted or substituted 5- or 6-membered heteroaryl,with the substituents of the aryl or heteroaryl group being as defined for R, linear or branched C_1-C_6-alkyl and C_5-C_6-cycloalkyl, in particular from the group consisting of O-R_{13} or S-R_{13} with R_{13} being selected from the group consisting of 5- or 6-membered aryl, and linear or branched C_1-C_4-alkyl.

[0012] It has been found that compounds of formula (I) are efficient in inhibiting β-secretase activity. Thus, such compounds are suitable in the treatment and prophylaxis of β-secretase activity related diseases such as Alzheimer's disease, Down's syndrome, and advanced aging of brain.

[0013] In presently slightly preferred inhibitors
R is independently from each other selected from H, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl, halogen, an -NR_2R_3 group wherein R_2 and R_3 are independently from each other H or linear or branched C_1-C_4-alkyl, or R_2 and R_3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle,
R' is independently from each other selected from the group consisting of hydrogen, halogen, in particular F, a C_1-C_4-alkyl group, an -NR_2R_3 group
wherein R_2 and R_3 are independently from each other H or linear or branched C_1-C_4-alkyl, or R_2 and R_3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, an amido group, an ester group, a



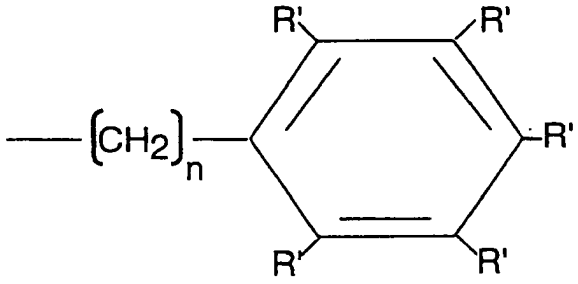
or two adjacent R' form a group



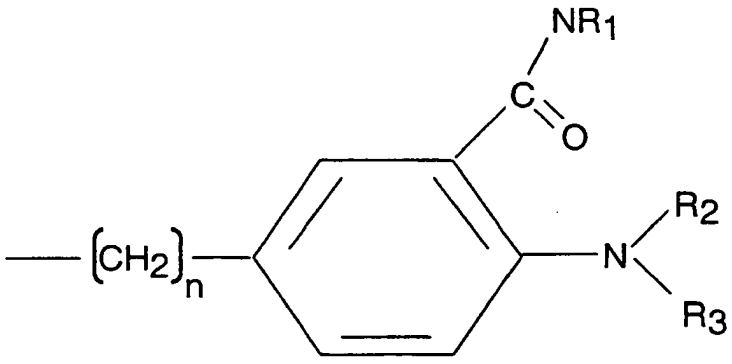
and

R_5 is independently from each other selected from C_1-C_4-alkylthio, aryl-C_1-C_4-alkylthio, aryloxy-C_1-C_4-alkyl, arylthio-C_1-C_4-alkyl, alkyloxy-C_1-C_4-alkyl, alkylthio-C_1-C_4-alkyl, C_1-C_4-alkyloxy, aryl-C_1-C_4-alkyloxy and optionally substituted linear or branched C_1-C_4-alkyl, preferably substituted linear or branched C_1-C_4-alkyl, with the substituent being selected from O-R_{13} or S-R_{13} with R_{13} being selected from the group consisting of 5- or 6-membered aryl, 5- or 6-membered heteroaryl, linear or branched C_1-C_4-alkyl and C_5-C_6-cycloalkyl.

[0014] Preferred is a Q that is

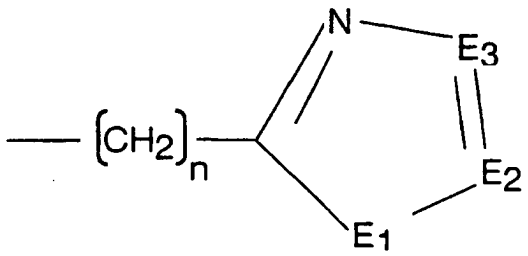


wherein R' and n are as defined above, and especially a Q selected from



wherein

R_1 is optionally substituted C_1-C_4-alkyl,
wherein the substituents are selected from optionally halogen substituted aryl, C_1-C_4-alkoxy, or morpholinyl,
R_2 = C_1-C_6-alkyl,
R_3 = C_1-C_6-alkyl,
or R_2 and R_3 form together with the nitrogen to which they are bound a 5-membered or a 6-membered aliphatic or aromatic ring, and
n = 0, 1 or 2, whereby in especially preferred embodiments
R_2 = C_1-C_4-alkyl, and
R_3 = C_1-C_4-alkyl,
or Q is



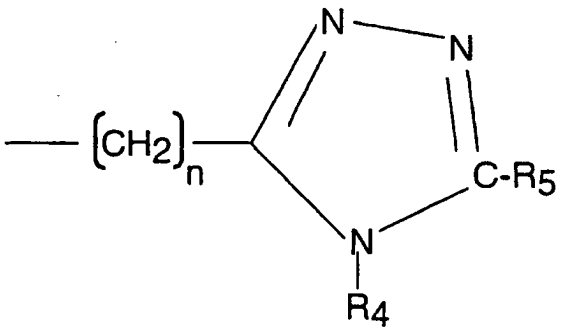
wherein

E_1 = NR_4 or S or O, wherein
R_4 is linear or branched C_1-C_4-alkyl,
E_2 = CR_5 or N, wherein
R_5 is C_1-C_4-alkylthio, aryl-C_1-C_4-alkylthio, aryloxy-C_1-C_4-alkyl,
E_3 = E_2 with the proviso that if E_2 is CR_5, E_3 is N and if E_2 is N, E_3 is CR_5, and
n is as defined above.

[0015] In a preferred embodiment
A = CR, wherein R is independently selected from H, CH_3, CH_2CH_3, OCH_3, $COCH_3$, Cl, Br, CF_3, more preferred selected from H, CH_3, CH_2CH_3, OCH_3, Cl, Br, CF_3.
[0016] In an also preferred embodiment, Q is 3-amido-4-amino-substituted phenyl a shown above with
R_1 = C_3-alkyl, C_1-C_4-alkoxy-C_2-C_3-alkyl, an optionally p-fluoro substituted phenyl-C_1-C_4-alkyl, and/or

$$R_2 = R_3 = -CH_3$$

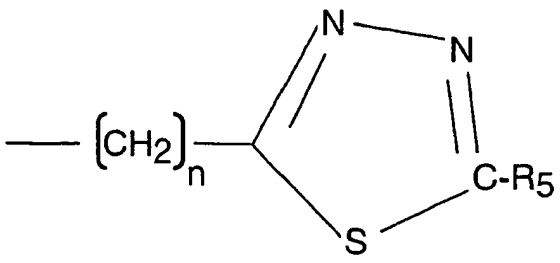
or Q is



wherein

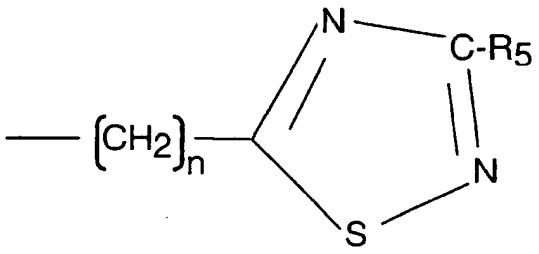
R_4 = linear or branched C_1-C_4-alkyl, in particular CH_3 or $-CH(CH_3)_2$

R_5 = C_1-C_4-alkylthio, and
n = 1 or 2,
or Q is



wherein

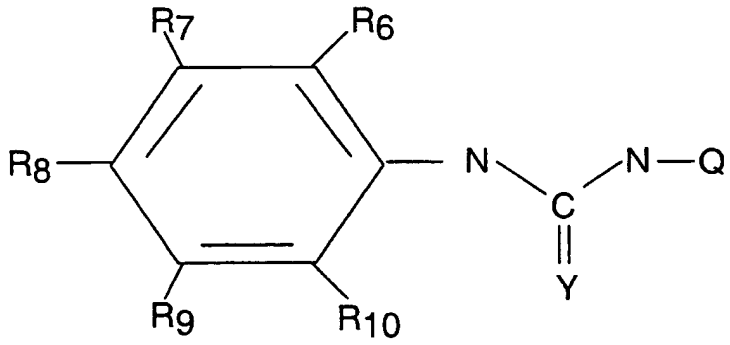
n = 0,
R_5 = aryloxy-C_1-C_4 alkyl, in particular phenoxy-C_1-C_4 alkyl, especially 1-phenoxy-ethyl,
or Q is



wherein

n = 0,
R_5 = C_1-C_4-alkylthio.

[0017] In a preferred embodiment, the compound is a compound of formula (II)



(II)

wherein

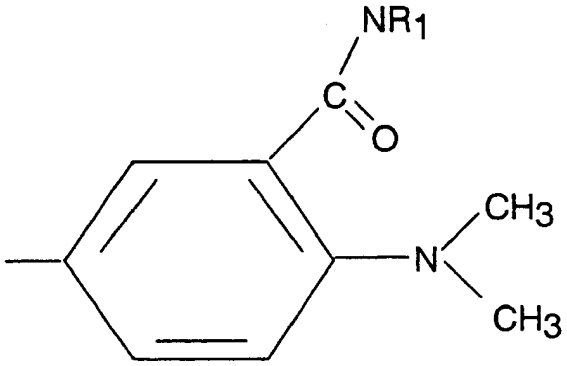
R_6 = H or halogen,
R_7 = H, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl, halo-C_1-C_4-alkyl or halogen,
R_8 = H, C_1-C_4-alkyl or halogen,
R_9 = H, C_1-C_4-alkyl, C_1-C_4-alkoxy or halo-C_1-C_4-alkyl,
R_{10} = H or halogen, and
Y and Q are as defined above.

[0018] In more preferred compounds of formula (II)

R_6 = H or Br,
R_7 = H, C1, CH_3, OCH_3, CO-CH_3, CF_3,
R_8 = H, CH_2CH_3, CH_3, C1,
R_9 = H, CH_3, OCH_3, CF_3, and
R_{10} = H, Br.

[0019] Also with regard to formula (II) Y and Q are as any Y and Q defined above with regard to formula (I) with the same preferences.

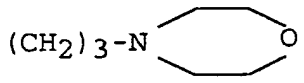
[0020] Especially preferred Q are



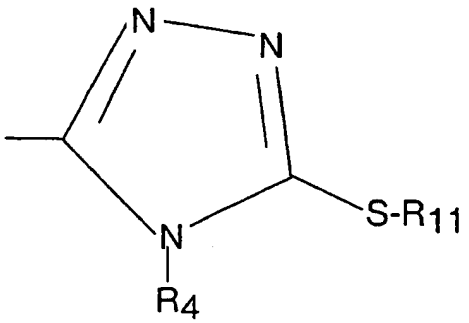
wherein

R_1 is optionally substituted C_1-C_4-alkyl,
wherein the substituents are selected from optionally halogen substituted aryl, C_1-C_4-alkoxy, morpholinyl
R_2 = C_1-C_4-alkyl
R_3 = C_1-C_4-alkyl, and
n = 0 or 1

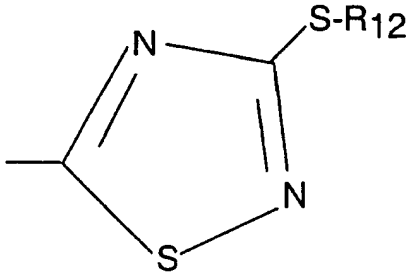
and preferably R_1 is $CH_2CH_2CH_3$, $(CH_2)_3$-OCH_3, $(CH_2)_2$-OCH_3, $(CH_2)_3$-OCH_2CH_3, CH_2CH_2-C_6C_5, p-F-benzyl, or



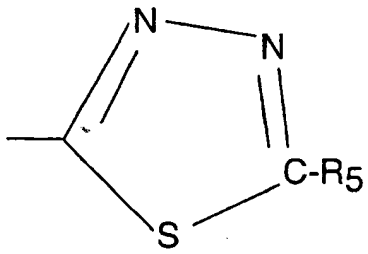
or Q is



wherein R_4 is CH_3, $CH(CH_3)_2$, and R_{11} is CH_3, CH_2CH_3, CH_2-C_6H_5,
or Q is



wherein R_{12} is CH_3 or CH_2CH_3, in particular CH_2CH_3
or Q is



wherein R_5 is $-(CH_2)_m(CR_{13})(OAr)$,
wherein R_{13} is H, C_1-C_4-alkyl, in particular methyl, Ar is phenyl or heteroaryl, in particular phenyl, and m = 0, 1 or 2.

[0021] As already mentioned above, the compounds of the present invention can be administered for prophylactic and/or therapeutic treatment of diseases related to the deposition of amyloid beta-protein, such as Alzheimer's disease, Down's syndrome, and advanced aging of the brain. In therapeutic applications, the compounds are administered to a host already suffering from the disease. The compounds will be administered in an amount sufficient to inhibit further deposition of senile plaques. The specific dose of compound(s) administered according to this invention to obtain therapeutic and/or prophylactic effects will, of course, be determined by the particular circumstances, such as the specific compound administered, the condition being treated, etc. A daily dose will contain a dosage level of from about 0.01 mg/kg to about 50 mg/kg of body weight of an active compound, preferably from about 0.05 mg/kg to about 20 mg/kg, for example from about 0.1 mg/kg to about 120 mg/kg.

[0022] The compound can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular and intranasal either as such, but preferable in a formulation comprising carriers adjuvants etc. Suitable pharmaceutically acceptable solid and liquid carriers and/or pharmaceutically acceptable adjuvants, such as stabilizing agents, emulsifyers, etc. are known in the art.

[0023] For example, a typical pharmaceutical composition for intramuscular injection would contain about one μg to one mg of the compound in from one to four milliliters of sterile buffered water. The typical pharmaceutical composition for intravenous infusion would contain about one to one hundred milligrams of the compound in from one hundred to five hundred milliliters of sterile Ringer's solution.

[0024] The pharmaceutical formulations are prepared by known procedures using known and readily available ingredients.

Short Description of the Drawings

[0025]

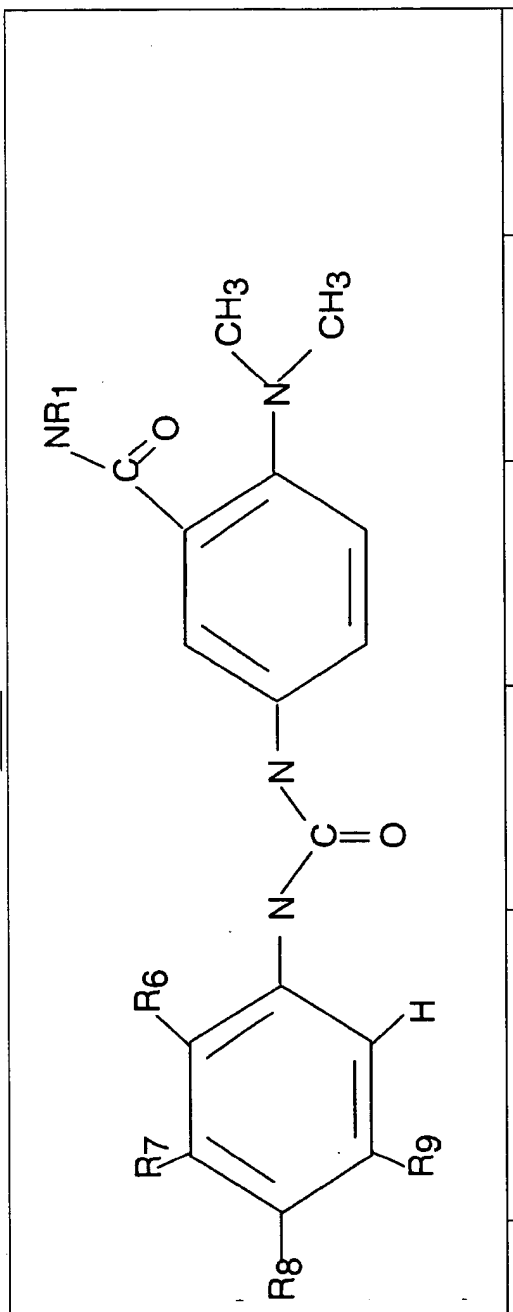
Figure 1 shows the structure formulas of compounds A1 to A14 of Tables 1 and 4
Figure 2 shows the structure formulas of compounds B1 to B4 of Tables 2 and 5
Figure 3 shows the structure formula of compounds C1 to C6 of Tables 3 and 6.

Modes for Carrying Out the Invention

[0026] Specific compounds and their β-secretase inhibiting effects are further described below.

[0027] Tables 1 to 3 make a relation between compound designation and structure.

Table 1:

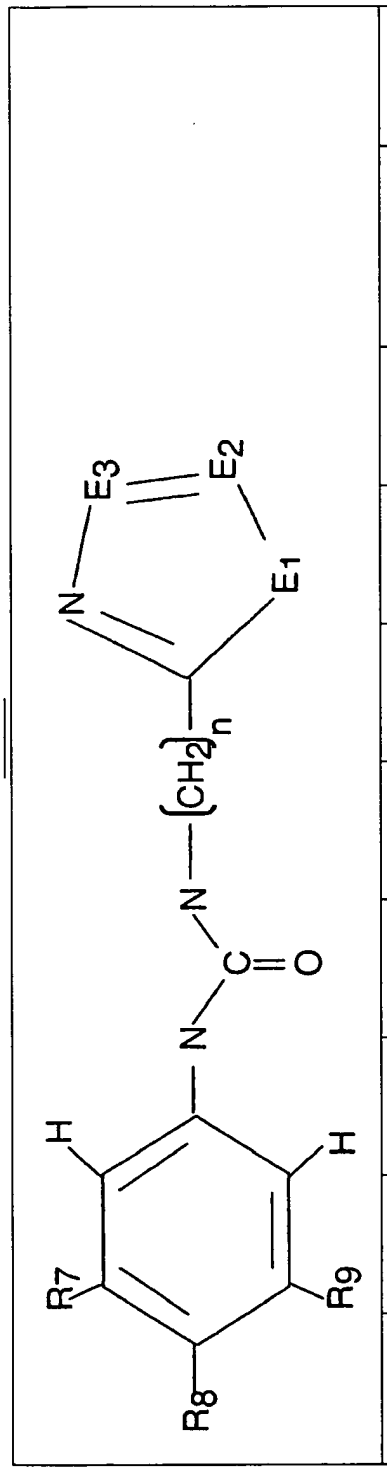


Compound	R_1	R_6	R_7	R_8	R_9
A1	$(CH_2)_3$-morpholin-4-yl	H	CF_3	H	CF_3
A2	$(CH_2)_3$-OCH_3	H	CF_3	H	CF_3
A3	$(CH_2)_3$-OCH_2CH_3	H	Cl	H	H
A4	$(CH_2)_3$-OCH_3	H	H	H	OCH_3
A5	$(CH_2)_2$-CH_3	H	H	H	OCH_3
A6	$(CH_2)_3$-morpholin-4-yl	H	H	CH_3	CH_3
A7	$(CH_2)_2$-OCH_3	H	CH_3	H	H
A8	$(CH_2)_2$-C_6H_5	H	CH_3	H	H

(continued)

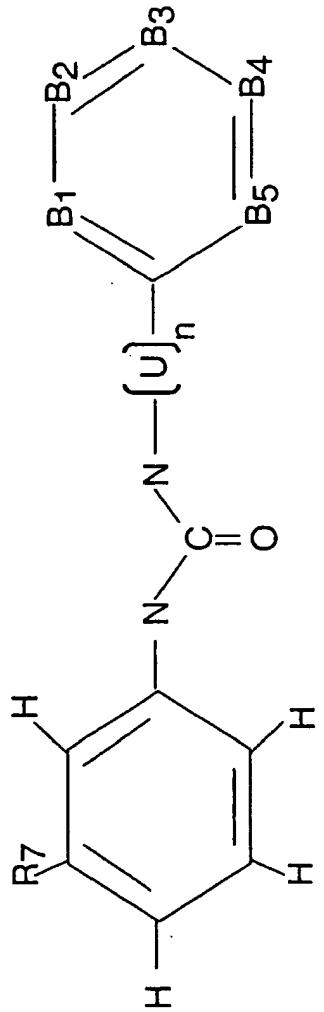
Compound	R_1	R_6	R_7	R_8	R_9
A9	$(CH_2)_3$-OCH_3	H	Cl	Cl	H
A10	CH_2-p-F-C_6H_4	H	OCH_3	H	OCH_3
A11	$(CH_2)_2$-CH_3	H	H	CH_2CH_3	H
A12	CH_2-p-F-C_6H_4	H	CF_3	H	CF_3
A13	$(CH_2)_3$-OCH_3	H	H	H	Br
A14	$(CH_2)_3OCH_2CH_3$	Br	H	H	H

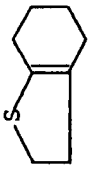
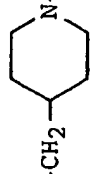
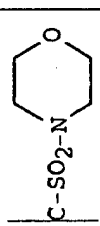
Table 2:



Compound	R_7	R_8	R_9	E_1	R_4	E_2	E_3	R_5	n
B1	CH_3	H	CH_3	NR_4	CH_3	CR_5	N	$S\text{-}CH_2\text{-}C_6H_5$	1
B2	CF_3	Cl	H	NR_4	$CH(CH3)2$	CR_5	N	$S\text{-}CH_3$	2
B3	H	H	$COCH_3$	S	-	N	CR_5	$S\text{-}CH_2CH_3$	0
B4	OCH_3	H	H	S	-	CR_5	N	$C(CH_3)(O\text{-}C_6H_5)$	0

Table 3:



Compound	R_7	-[U]n-	B_1	B_2	B_3	B_4	B_5
C1	OCH_3	$-(CH_2)_2NH-$	N	CCH_3	N		
C2	H	$-(CH_2)_2NH-$	N	CCH_3	N		
C3	CH_3		CH	CH		CH	CH
C4	H	$-(CH_2)_2O-$	N		N	$C-N(CH_3)_2$	N
C5	H	$-(CH_2)_2O-$	N	$CNH(CH_2CH_3)$	N	$C-NHC(CH_3)_3$	N
C6	$COCH_3$		CH	CH	CF	CH	CH

[0028] These compounds have been tested for their performance as β-secretase inhibitors.

[0029] The results of three different tests performed are listed in Tables 4 to 6 below.

[0030] The tests performed were

a) Aβ1-40 (Sw) bioassay, which measures the amount of the amyoid peptide Aβ1-40 in the supernatant of Swedish APP695 transgenic HEK293 cells in the presence of the various BACE inhibitors via ELISA (enzyme-linked immunosorbent assay). In the table, the inhibitory concentration that reduces Aβ1-40 secretion to 50 % is indicated (IC50), or the % reduction of Aβ1-40 secretion at the indicated concentration.

b) SEAP bioassay, which measures the amount of the secreted reporter enzyme SEAP (secreted alkaline phosphatase) in the supernatant of transiently transfected HEK293 cells. A SEAP-APP(Sw)695 fusion protein is transiently expressed in HEK293 cells in the presence of the various BACE inhibitors. Secretion of the SEAP moiety upon cleavage at the APP β-site is quantitated via a luminescence readout. In the table, the inhibitory concentration that reduces secreted SEAP activity to 50 % is indicated (IC50), or the % reduction of secreted SEAP activity at the indicated concentration.

c) FRET assay, which measures the activity of recombinant BACE enzyme in the presence of the various BACE inhibitors via a FRET (fluorescence resonance energy transfer)-based readout. In the table, the inhibitory concentration that reduces the activity of BACE to 50 % is indicated (IC50), or the % reduction of the activity of BACE at the indicated concentration.

d) An additional in silico test was performed for the compounds listed in Tables 1 to 3. The compounds were docked with the FFLD approach (Budin et al., Biol. Chem. 382, 1365-1372, 2001) and their binding energy was evaluated with the LIECE method (Huang and Caflisch, J. Med. Chem. 47, 5791-5797, 2004). The affinity evaluated with LIECE is in the low micromolar range for most of these compounds.

Table 4

Compo und	Aβ1-40 (Sw) bioassay (cell- based)	SEAP bioassay (cell-based)	FRET assay (in vitro)	LIECE Ki[μM]
A1	IC50 3.0 μM	IC50 3.5 μM	IC50 58 μM	8.11
A2	IC50 3.2 μM	27 (3 μM)	IC50 284 μM	9.35
A3	IC50 2.6 μM	23 (3 μM)	IC50 97 μM	9.81
A4	IC50 7.5 μM	21 (6 μM)	33 (100 μM)	10.26
A5	IC50 14.3 μM	0 (6 μM)	16 (100 μM)	15.99
A6	IC50 23 μM	19 (12.5 μM)	21 (100 μM)	17.56
A7	IC50 12.9 μM	0 (12.5 μM)	0 (100 μM)	18.64
A8	IC50 5.6 μM	14 (3 μM)	35 (100 μM)	32.34
A9	IC50 5.9 μM	17 (3 μM)	IC50 46 μM	32.56
A10	IC50 3.1 μM	10 (1.6 μM)	IC50 64 μM	34.71
A11	IC50 5.2 μM	0 (6 μM)	20 (200 μM)	38.37
A12	IC50 4.2 μM	14 (1.6 μM)	IC50 131 μM	39.41
A13	IC50 3.8 μM	25 (3 μM)	37 (100 μM)	50.09
A14	IC50 7.8 μM	0 (6 μM)	0 (100 μM)	66.41

Table 5:

Compo und	Aβ1-40 (Sw) bioassay (cell-based)	SEAP bioassay (cell-based)	FRET assay (in vitro)	LIECE Ki[μM]
B1	IC50 18 μM	0 (50 μM)	0 (500 μM)	11.85
B2	IC50 40 μM	0 (12.5 μM)	0 (250 μM)	28.53
B3	IC50 1.6 μM	IC50 10 μM	0 (25 μM)	29.60
B4	IC50 13 μM	0 (12.5 μM)	0 (500 μM)	34.97

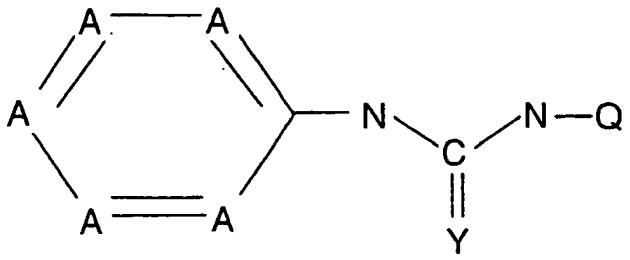
Table 6:

Compo und	Aβ1-40 (Sw) bioassay (cell-based)	SEAP bioassay (cell-based)	FRET assay (in vitro)	LIECE Ki[μM]
C1	21 (6 μM)	0 (12.5 μM)	0 (500 μM)	15.37
C2	IC50 13 μM	0 (12.5 μM)	0 (500 μM)	33.69
C3	IC50 22 μM	0 (12.5 μM)	0 (50 μM)	15.96
C4	31 (12.5 μM)	0 (12.5 μM)	0 (500 μM)	23.49
C5	IC50 10-20 μM	0 (25 μM)	0 (500 μM)	32.95
C6	22 (25 μM)	IC50 35 μM	IC50 490 μM	48.10

[0031] While there are shown and described presently preferred embodiments of the invention, it is to be distinctly understood that the invention is not limited thereto but may be otherwise variously embodied and practiced within the scope of the following claims.

Claims

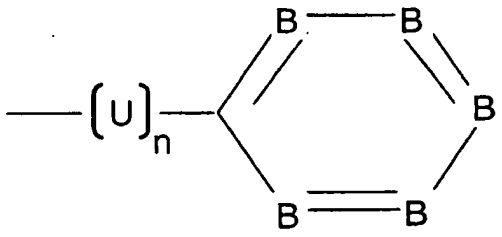
1. β-secretase inhibitors of formula I



(I)

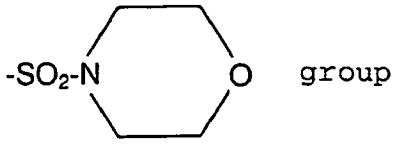
wherein

A = N or CR wherein
R is independently from each other selected from H, C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkyl, C_1-C_6-alkyl-carbonyl, halogen, an -NR_2R_3 group wherein R2 and R3 are independently from each other H, linear or branched C1-C6-alkyl, in particular linear or branched Cl-C4-alkyl, or R2 and R3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, and wherein
Y = O or S
Q = an aromatic group or an araliphatic group having the following formula



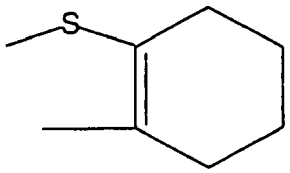
wherein

B = N or CR', wherein
R' is independently from each other selected from the group comprising hydrogen, halogen, in particular F, a C_1-C_6-alkyl group, in particular a C_1-C_4-alkyl group, an $-NR_2R_3$ group wherein R2 and R3 are independently from each other H, linear or branched Cl-C6-alkyl, in particular linear or branched C1-C4-alkyl, or R2 and R3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, an amido group, an ester group, a



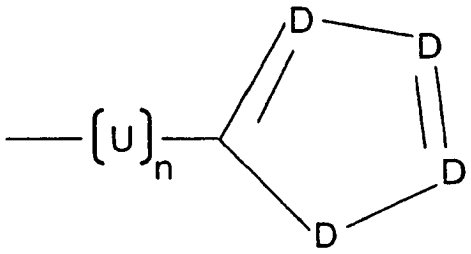
group

or two adjacent R' form the group



-U- = $-CH_2-$, C=O, $-(CH_2)_nS-$, $-(CH_2)_nO-$, $-(CH_2)_nNH-$, or

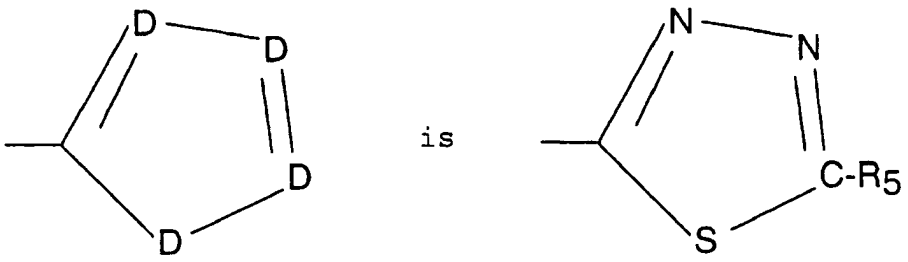
wherein the heterocycle is optionally substituted, in particular by one or two C_1-C_4-alkyl groups, or such that a bicycle is formed, and
n independently from each other is 0, 1 or 2
or Q has the following formula



wherein

D = O or S or N or NR_4 or CR_5, wherein
R_4 is linear or branched C_1-C_6-alkyl, in particular C_1-C_4-alkyl
R_5 is independently from each other selected from C_1-C_6-alkylthio, aryl-C_1-C_6-alkylthio, aryloxy-C_1-C_6-alkyl, arylthio-C_1-C_6-alkyl, alkyloxy-C_1-C_6-alkyl, alkylthio-C_1-C_6-alkyl, C_1-C_6-alkyloxy, aryl-C_1-C_6-alkyloxy and optionally substituted linear or branched C_1-C_6-alkyl,
U and n are as defined above,

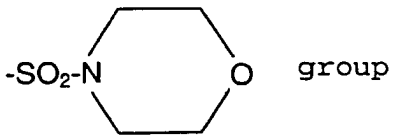
or pharmaceutically acceptable salts thereof
as pharmaceutical, with the proviso that in the case that n is 0 and



R_5 is substituted linear or branched C_1-C_6-alkyl, preferably linear or branched C_1-C_4-alkyl, with the substituent being selected from O-R_{13} or S-R_{13} or N-$R_{13}R_{13}$'with R_{13} and R_{13}' being independently selected from the group consisting of unsubstituted or substituted 5- or 6-membered aryl, unsubstituted or substituted 5- or 6-membered heteroaryl, with the substituents of the aryl or heteroaryl group being as defined for R, linear or branched C_1-C_6-alkyl and C_5-C_6-cycloalkyl, in particular from the group consisting of O-R_{13} or S-R_{13} with R_{13} being selected from the group consisting of 5- or 6-membered aryl, and linear or branched C_1-C_4-alkyl.

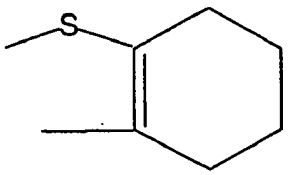
2. The β-secretase inhibitors of claim 1, wherein

R is independently from each other selected from H, C_1-C_4-alkyl, C_1-C_4-alkoxy, halo-C_1-C_4-alkyl, C_1-C_4-alkylcarbonyl, halogen, an -NR_2R_3 group wherein R_2 and R_3 are independently from each other H or linear or branched C_1-C_4-alkyl, or R_2 and R_3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle,
R' is independently from each other selected from the group consisting of hydrogen, halogen, in particular F, a C_1-C_4-alkyl group, an -NR_2R_3 group
wherein R_2 and R_3 are independently from each other H or linear or branched C_1-C_4-alkyl, or R_2 and R_3 form together with the nitrogen to which they are bound an aliphatic or aromatic 5- or 6-membered one or more heteroatoms comprising heterocycle, an amido group, and an ester group, a



group

or two adjacent R' form a group

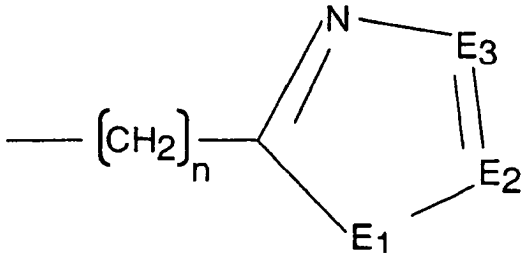


, and

R_5 is independently from each other selected from C_1-C_4-alkylthio, aryl-C_1-C_4-alkylthio, aryloxy-C_1-C_4-alkyl, arylthio-C_1-C_4-alkyl, alkyloxy-C_1-C_4-alkyl, alkylthio-C_1-C_4-alkyl, C_1-C_4-alkyloxy, aryl-C_1-C_4-alkyloxy and optionally substituted linear or branched C_1-C_4-alkyl, preferably substituted linear or branched C_1-C_4-alkyl, with the substituent being selected from OR_{13} or S-R_{13} with R_{13} being selected from the group consisting of 5- or 6-membered aryl, 5- or 6-membered heteroaryl, linear or branched C_1-C_4-alkyl and C_5-C_6-cycloalkyl.

3. The β-secretase inhibitors of claim 1 or 2
wherein Q is an aromatic or araliphatic group as defined above or

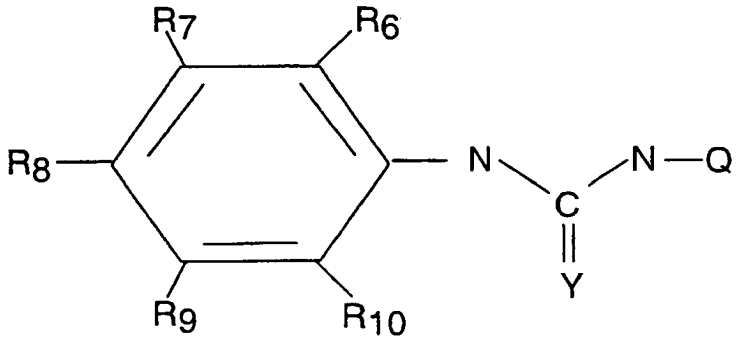
Q is



wherein

E_1 = NR_4 or S or O, wherein
R_4 is linear or branched C_1-C_4-alkyl,
E_2 = CR_5 or N, wherein
R_5 is C_1-C_4-alkylthio, aryl-C_1-C_4-alkylthio, aryloxy-C_1-C_4-alkyl,
E_3 = E_2 with the proviso that if E_2 is CR_5, E_3 is N and if E_2 is N, E_3 is CR_5, and
n is as defined above.

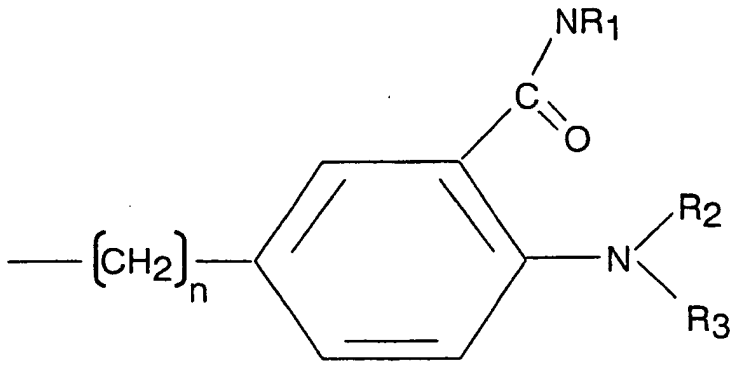
4. The β-secretase inhibitors of anyone of the preceding claims with formula II



(II)

wherein

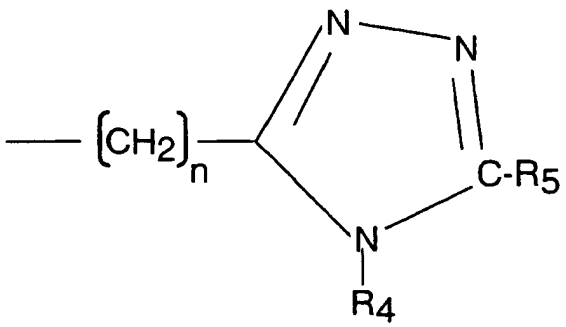
R_6 = H or halogen
R_7 = H, C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylcarbonyl, halo-C_1-C_4-alkyl or halogen,
R_8 = H, C_1-C_4-alkyl or halogen,
R_9 = H, C_1-C_4-alkyl, C_1-C_4-alkoxy or halo-C_1-C_4-alkyl,
R_{10} = H or halogen
Y and Q are as defined above, and
wherein Q is a group of the following formula



wherein

R_1 is optionally substituted C_1-C_4-alkyl,
wherein the substituents are selected from optionally halogen substituted aryl, C_1-C_4-alkoxy, morpholinyl,
R_2 = C_1-C_6-alkyl,
R_3 = C_1-C_6-alkyl, or
R2 and R3 form together with the nitrogen to which they are bound a 5-membered or a 6-membered aromatic or aliphatic heterocycle, and
n = 0, 1 or 2,

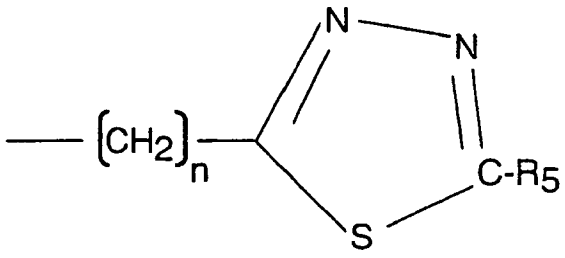
or Q is a group of the following formula



wherein

R_4 = linear or branched C_1-C_4-alkyl, in particular CH_3 or $CH(CH_3)_2$,
R_5 = is C_1-C_4-alkylthio or aryl-C_1-C_4-alkylthio, and
n = 1 or 2,

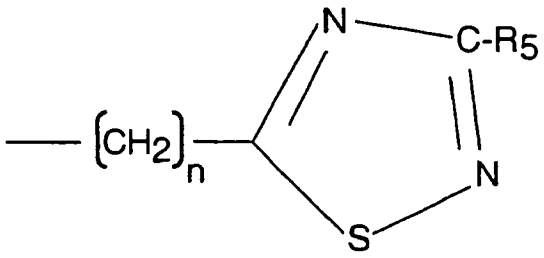
or Q is a group of the following formula



wherein

n = 0,
R_5 = aryloxy-C_1-C_4 alkyl, in particular phenoxy-C_1-C_4 alkyl, especially 1-phenoxy-ethyl,

or Q is a group of the following formula



wherein

n = 0,
R_5 = C_1-C_4 alkylthio,

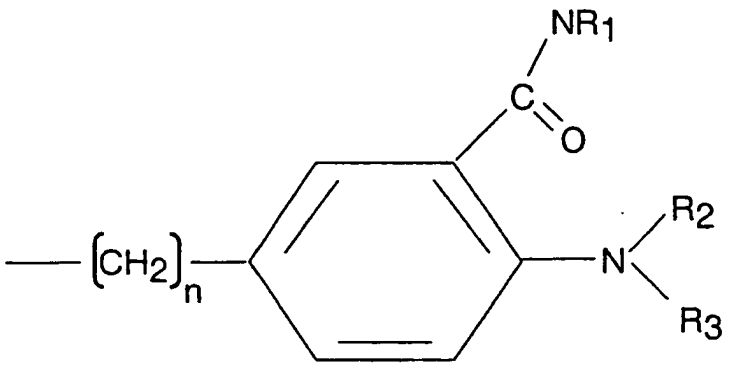
or pharmaceutically acceptable salts thereof.

5. The β-secretase inhibitor of claim 4 wherein

R_6 = H or Br,
R_7 = H, Cl, CH_3, OCH_3, CO-CH_3, CF_3,
R_8 = H, CH_2CH_3, CH_3, Cl,
R_9 = H, CH_3, OCH_3, CF_3,
R_{10} = H, Br,

or pharmaceutically acceptable salts thereof.

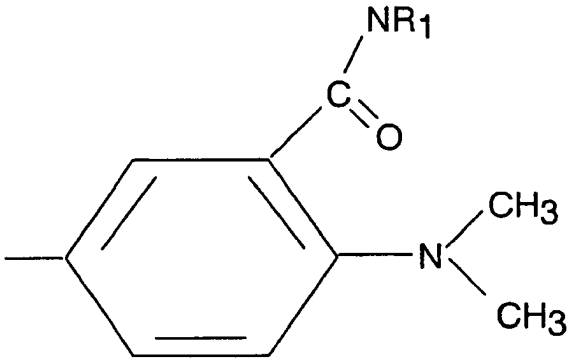
6. The β-secretase inhibitor of claim 4 or 5 wherein Q is a group of the following formula



wherein

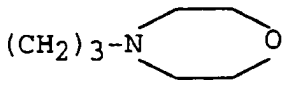
R_1 is optionally substituted C_1-C_4-alkyl,
wherein the substituents are selected from optionally halogen substituted aryl, C_1-C_4-alkoxy, morpholinyl,
R_2 = C_1-C_4-alkyl,
R_3 = C_1-C_4-alkyl, and
n = 0 or 1.

7. The β-secretase inhibitor of claim 6,
wherein Q is

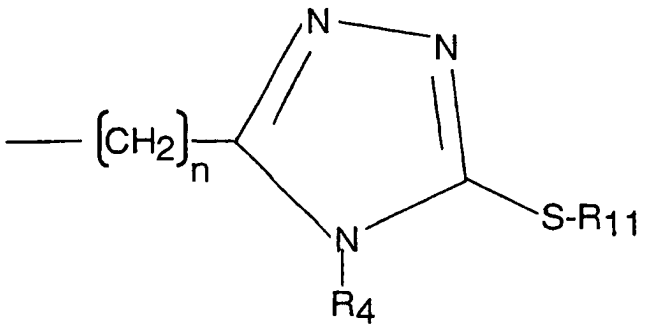


or pharmaceutically acceptable salts thereof.

8. The β-secretase inhibitor of claim 7,
wherein R_1 is $CH_2CH_2CH_3$, $(CH_2)_3$-OCH_3, $(CH_2)_2$-OCH_3, $(CH_2)_3$-OCH_2CH_3, CH_2CH_2-C_6C_5, CH_2-p-F-C_6H_4, or



9. The β-secretase inhibitor of claim 4 or 5,
wherein Q is

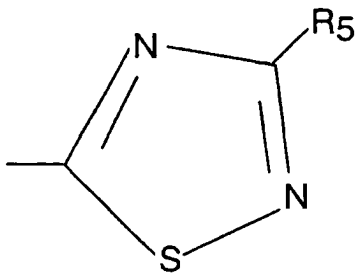


and wherein

n is 1 or 2,
R_4 is CH_3, $CH(CH_3)_2$, and
R_{11} is CH_3, CH_2CH_3, CH_2-C_6H_5,

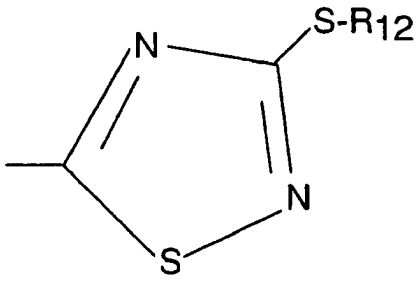
or pharmaceutically acceptable salts thereof.

10. The β-secretase inhibitor of claim 4 or 5, wherein Q is



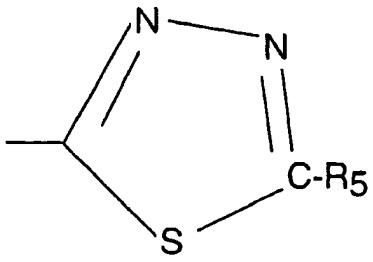
and wherein R_5 is as defined above,
or pharmaceutically acceptable salts thereof.

11. The β-secretase inhibitor of claim 10,
wherein Q is



wherein R_{12} is CH_3 or CH_2CH_3, in particular CH_2CH_3,
or pharmaceutically acceptable salts thereof.

12. The β-secretase inhibitor of claim 4 or 5, wherein Q is



and wherein R_5 is as defined above,
or pharmaceutically acceptable salts thereof.

13. The β-secretase inhibitor of claim 12
wherein R_5 is $(CH_2)_m$-(CR_{13}) (OAr)
wherein R_{13} is H, C_1-C_4-alkyl, in particular methyl, Ar is phenyl or heteroaryl, in particular phenyl, and m = 0, 1 or 2, or pharmaceutically acceptable salts thereof.

14. Use of a β-secretase inhibitor of anyone of the preceding claims, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for inhibiting the production and/or the accumulation of amyloid beta-protein in warm blooded mammals, in particular human beings, especially for the treatment of Alzheimer's disease and or Down's syndrome and/or aging of brain.

15. A pharmaceutical composition comprising at least one β-secretase inhibitor of anyone of claims 1 to 13, or a pharmaceutically acceptable salt thereof, together with a pharmaceutically acceptable carrier and optionally one or more adjuvants.

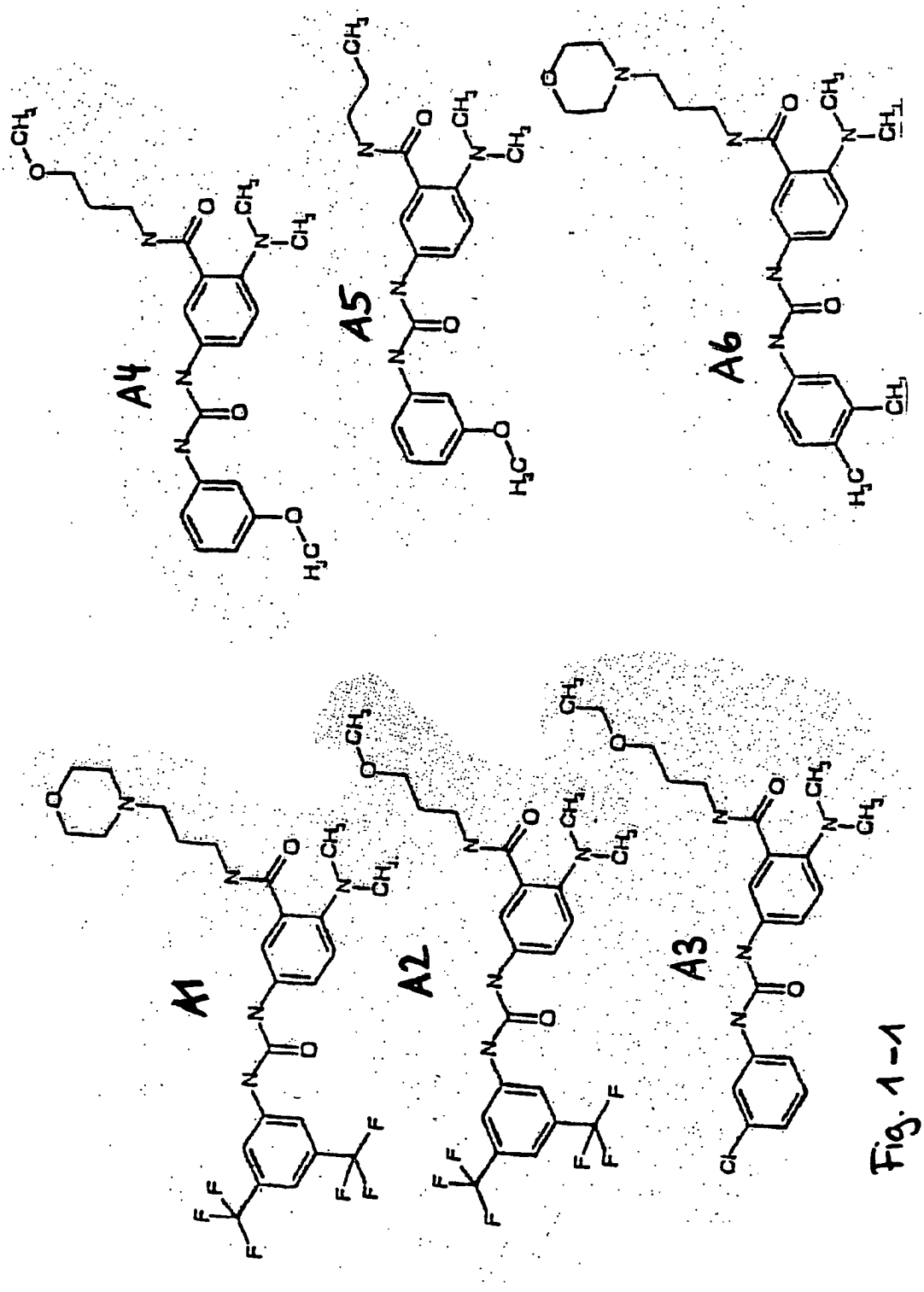


Fig. 1-1

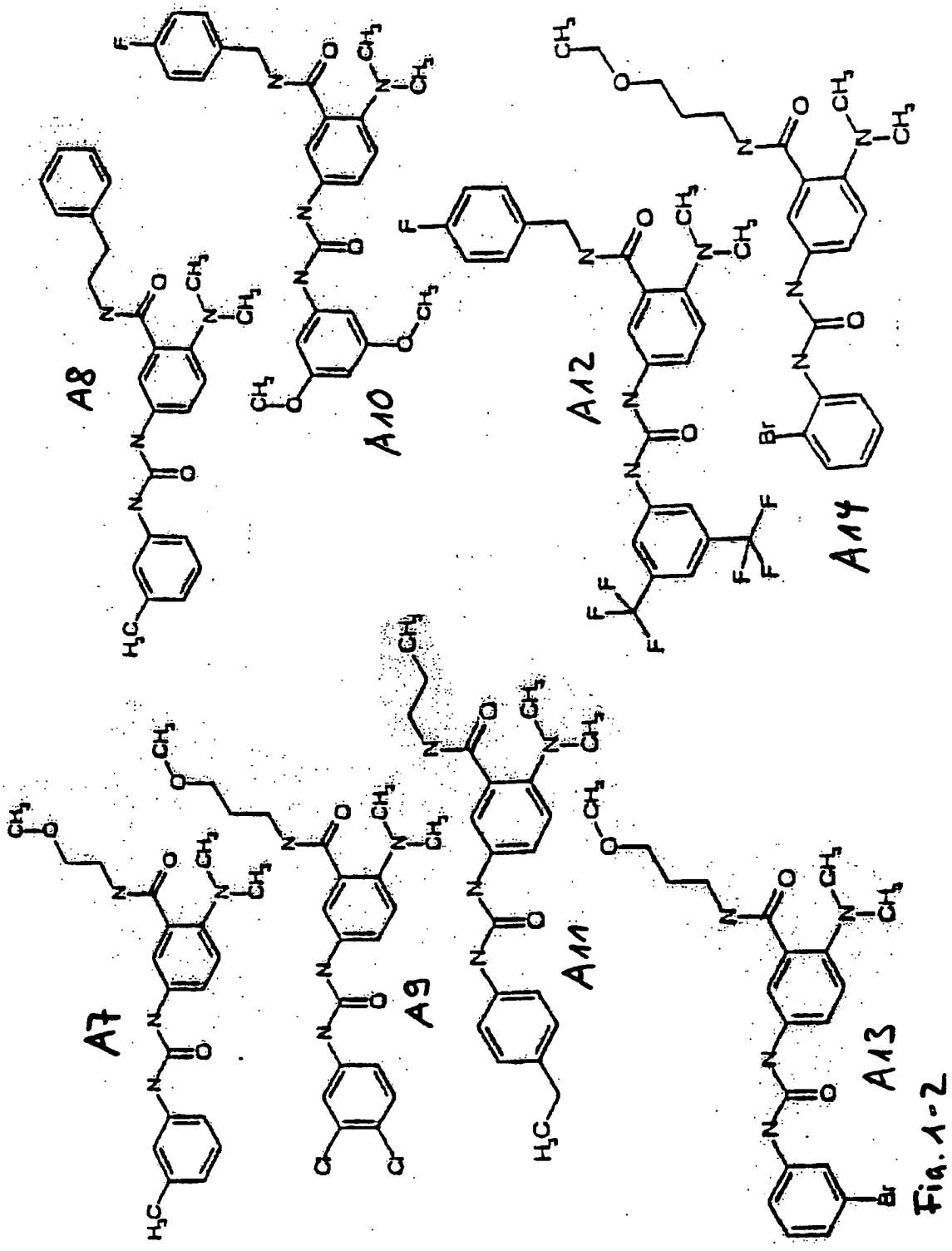
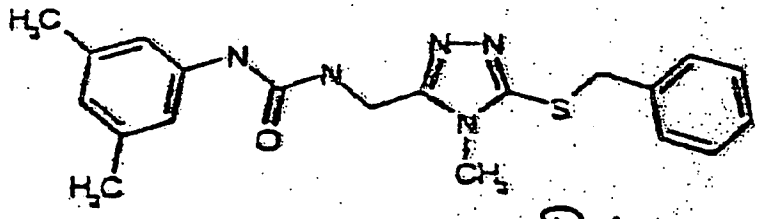
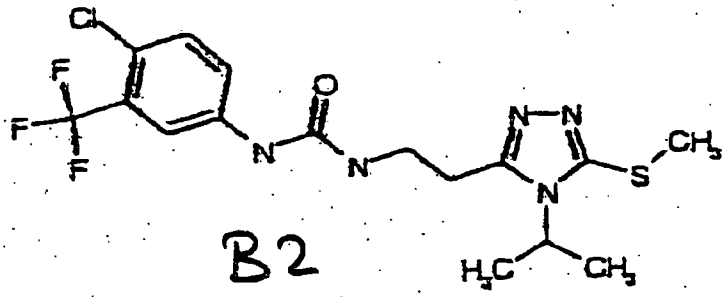


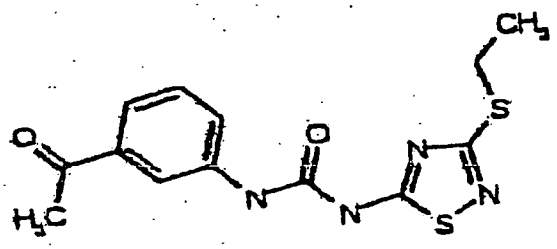
Fig. 1-2



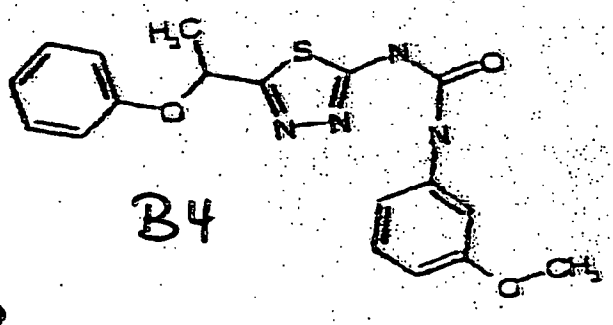
B1



B2



B3



B4

Fig. 2

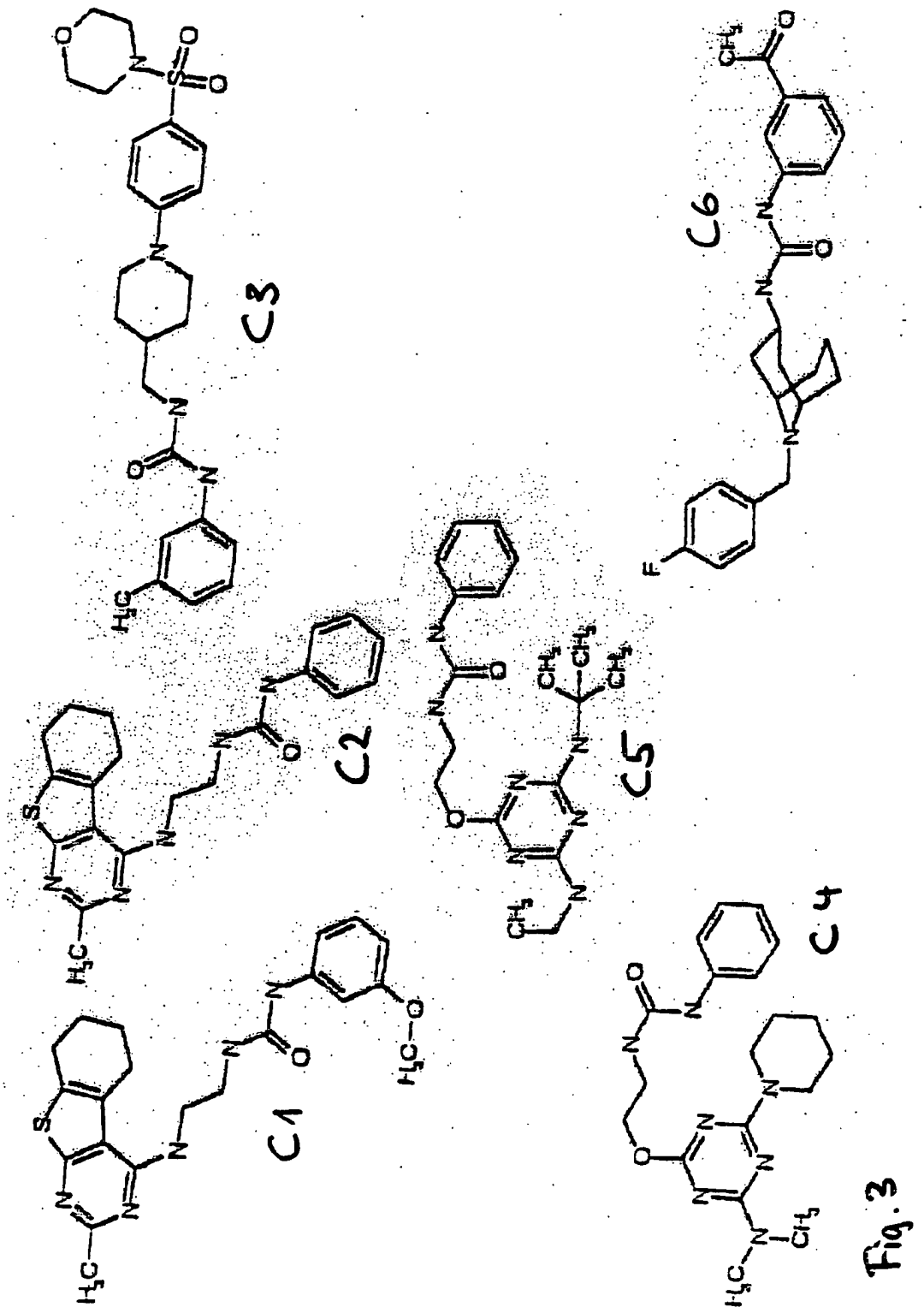


Fig. 3

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which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application Number EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
D,X	US 5 814 646 A (HEINZ ET AL) 29 September 1998 (1998-09-29) * column 1, line 20 - line 48 * -----	1-15	C07D295/12 C07C275/40 C07D249/12 C07D285/08
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002350888 * order numbers: ASN 10345176, ASN 10344816, ASN 10344636, ASN 10344528 * & "INTERCHIM INTERMEDIATES" 18 January 2005 (2005-01-18), INTERCHIM , 211 BIS AV J.F. KENNEDY, BP 1140, MONTLUCON, 03103, FRANCE ----- -/--	1-4,9	C07D295/22 C07D251/52 C07D495/04 C07D471/08 A61K31/17 A61K31/53 A61P25/28

TECHNICAL FIELDS SEARCHED (Int.Cl.7)

C07C
C07D
A61K
A61P

INCOMPLETE SEARCH

The Search Division considers that the present application, or one or more of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for these claims.

Claims searched completely :

Claims searched incompletely :

Claims not searched :

Reason for the limitation of the search:

see sheet C

Place of search	Date of completion of the search	Examiner
The Hague	4 November 2005	Fitz, W

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
O : non-written disclosure
P : intermediate document

T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
D : document cited in the application
L : document cited for other reasons

& : member of the same patent family, corresponding document

EPO FORM 1503 03.82 (P04C07)

European Patent Office

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Application Number
EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002350890 * CGX 3006286, 3006283, 3006617, 3006175, 3006399, 3006653, 3006384, 3006870, 3006564, 3006319, 3006239, 3006367, 3006368, 3006847, 3006220, 3006245, 3006316, 3006317, 3006219, 3006023, 3006774, 3006541, 3006037, 3006623, 3006469, 3006533, 3006455, 3006224, 3006173, 3005918, 3006570, 3005801, 3006320, 3005885, 3006382, 3006655, 3006726, 3006372, 3006622, 3006620, 0740976, 3006379, 3006401, 3006365, 3006171, 3006733, 3006329, 3006693, 3006282, 3006350, 3006053, 3006612, 3006197, 3006656, 3006468, 3006234, 3006288, 3006508, 3006671, 3006645, 3006672, 3006257, 3006715, 3006590, 3006354, 3006687, 3006309, 3006187, 3006272, 3006036, 3006255, 3005823, 3006459, 3006461, 3006066, 3006351, 3006629, 3005816, 3006235, 3005802, 3006344, 3006248, 3005909, 3006852, 3006599, 3006603, 3006605, 0741352, 3006402, 0733817, 3006686, 3006342, 3006334, 3006216, 3005910, 3006335, 3006261, 3006246, 3006253, 3006198, 3005898, 3006311, 3005906, 3006215, 3005903, 3006028, 3006330, 3005884, 3005807, 3006043, 3005822, 3006205, 0731601, 3006229, 3006589, 3006268, 3006624, 3006571, 3006584, 3006210 * -/--	1-8	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
	& "COMGENEX PRODUCT LIST" 15 April 2005 (2005-04-15), COMGENEX INTERNATIONAL INC. , PRINCETON CORPORATE PLAZA IV, 11 DEER PARK DRIVE, STE. 210, MONMOUTH, NJ, 08852, US -----		
X	DATABASE CHEMCATS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; XP002350889 * ASN 10348177, ASN 10348171, ASN 10348141, ASN 10348130, ASN 10348112, ASN 10347817, ASN 10347751, ASN 10345176, ASN 10344816, ASN10344636, ASN 10344528, ASN 10344487 * & "ASINEX EXPRESS PLATINUM COLLECTION" 21 February 2005 (2005-02-21), ASINEX , 5 GABRICHEVSKOGO ST. BLDG 8, MOSCOW, 123367, RUSSIA -----	1-4,9	TECHNICAL FIELDS SEARCHED (Int.Cl.7)
X	HELAL C J ET AL: "Discovery and SAR of 2-aminothiazole inhibitors of cyclin-dependent kinase 5/p25 as a potential treatment for Alzheimer's disease" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 14, no. 22, 15 November 2004 (2004-11-15), pages 5521-5525, XP004598586 ISSN: 0960-894X * title * * page 5522, table 1, compound 5 * -----	1,14,15	
A	WO 03/087842 A (ESBATECH AG; BARBERIS, ALCIDE; MIDDENDORP, OLIVER, MICHAEL; LUETHI, UR) 23 October 2003 (2003-10-23) * claim 1 * -----	1,14,15	
	-/--		

EPO FORM 1503 03.82 (P04C10)

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

Application Number
EP 05 01 2616

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	CUMMING J N ET AL: "DESIGN AND DEVELOPMENT OF BACE-1 INHIBITORS" CURRENT OPINION IN DRUG DISCOVERY AND DEVELOPMENT, CURRENT DRUGS, LONDON, GB, vol. 7, no. 4, July 2004 (2004-07), pages 536-556, XP009039538 ISSN: 1367-6733 * the whole document * -----	1,14,15	TECHNICAL FIELDS SEARCHED (Int.Cl.7)

7

EPO FORM 1503 03.82 (P04C10)

European Patent Office

INCOMPLETE SEARCH SHEET C

Application Number
EP 05 01 2616

Claim(s) searched completely:
4-13

Claim(s) searched incompletely:
1-3,14,15

Claim(s) not searched:
-

Reason for the limitation of the search:

The present claims 1-3 and 14,15 relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 84 and 83 EPC is to be found however for only a very small proportion of the compounds claimed. For example, formula (I) includes compounds with a series of nitrogen atoms attached to each other which are commonly known to be unstable. Also, formula (I) is so broad that trivial and commonly known compounds such as diphenylurea are included in the claimed scope. The non-compliance with the substantive provisions is to such an extent, that a meaningful search of the whole claimed subject-matter of the claim could not be carried out (Rule 45 EPC and Guidelines B-VIII, 3). The extent of the search was consequently limited.

The search of claims 1-3 and 14,15 was restricted to the compounds which appear to be supported and a generalisation of their structural formulae, i.e. the compounds of claim 4 and their use.

ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 05 01 2616

This annex lists the patent family members relating to the patent documents cited in the above-mentioned European search report. The members are as contained in the European Patent Office EDP file on
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04-11-2005

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WO 03087842 A	23-10-2003	AU 2002253468 A1	27-10-2003
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		EP 1495329 A1	12-01-2005

EPO FORM P0459

For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

REFERENCES CITED IN THE DESCRIPTION

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- US 5814646 A **[0007]**
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- **BUDIN et al.** *Biol. Chem.*, 2001, vol. 382, 1365-1372 **[0030]**
- **HUANG ; CAFLISCH.** *J. Med. Chem.*, 2004, vol. 47, 5791-5797 **[0030]**